REMARKS

Applicants have amended claim 2 to correct two typographical errors.

Claims 1-2, 5-9 and 18-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5-8, 11 of copending Application No. 10/269,027 (now U.S. Pat. No. 7,273,623).

Submittted herewith is Applicants' terminal disclaimer with regard to U.S. Pat. No. 7,273,623.

Applicant acknowledges the obligation under 37 C.F.R. 1.56 to point out the inventor and the invention dates of each claim that was not commonly owned at the time a later invention was made. The Examiner is correct in presuming that the subject matter of the claims in the present application was commonly owned at the time any inventions covered therein were made.

Claims 1-2, 5-21 are rejected under 35 USC 103(a) as being unpatentable over *Patel et al.* (U.S. 6,248,363) in view of *Gordziel* (U.S. 6,037,358).

The Examiner indicates that *Patel et al.* disclose the general teachings of converting of one of the active pharmaceutical ingredients (hydrophilic, amphiphilic or hydrophobic) such as gabapentin (see col. 5, line 46) into its tannate salt complex (see col. 40, line 7) as a salt of a pharmaceutically acceptable cation (see col.39, line 65).

Applicants assert that the *Patel et al.* reference is not relevant to the present application. The invention in the *Patel et al.* patent is a solid pharmaceutical composition for a wide variety of pharmaceutical active ingredients combined with an effective solubilizing amount of a hydrophilic surfactant and a lipophilic additive so that the pharmaceutical active ingredient is either partially or fully solubilized.

Patel et al. has nothing to do with the formation of pharmaceutically active ingredients as tannate salts.

Gabapentin is listed as a 1 out of 68 preferred hydrophobic active ingredients. Gabapentin, by the way, is hydrophilic (see Merck Index, 13th Edition, 2001, in Appendix I), however, the *Patel et al.* patent indicates that potential active ingredients also include hydrophilic ones.

Tannic acid is merely listed as 1 of about 30 to 40 acids that can be used as a bufferant, see col. 39, lines 43 and 54, and col. 40, line 7. There is nothing in the *Patel et al.* disclosure that gives a reasonable expectation that one of ordinary skill in the art would be able to prepare a gabapentin tannate salt.

The Examiner is factually incorrect when he states that *Patel et al.* expressly disclose that it seems reasonable to convert the active pharmaceutical ingredients such as chlorpheniramine (see col. 5, line 34) and gabapentin (see col. 5, line 46) into its tannate salt complex. *Patel et al.* discloses nothing at all with regard to the formation of chlorpheniramine or gabapentin tannate salts. *Patel et al.* offer a laundry list of many active ingredients which can be used with their hydrophilic and lipophilic surfactants to improve the solubility, stability, absorption and/or bioavailability of the pharmaceutical active ingredients. Tannic acid is listed merely as a bufferant.

With regard to *Gordziel*, the Examiner indicates that *Gordziel* discloses a process of preparing antihistamine tannates; for example, chlorpheniramine tannate can be obtained from reacting chlorpheniramine with tannic acid in the presence of isopropanol (see col. 1, lines 64-67).

Applicants agree. Significantly, however, the process set forth in *Gordziel* and the alternate routes mentioned in col. 2, lines 1 & 2, relate to the preparation of antihistamine tannates with no mention or suggestion of the preparation of gabapentin tannate (gabapentin is an anti-convulsant).

Gordziel discloses the novel combination of phenylephrine tannate and chlorpheniramine tannate where MAS is used only as an excipient in the preparation of a suspension formulation. See Example 2. It has nothing to do with the use of MAS in the formation of the actual active pharmaceutical ingredient (API) tannate salt complex.

The Examiner also states that chlorpheniramine is equivalent to gabapentin for the purpose of preparing tannate salts. Attached as Appendix II are excerpts from The Merck Index, pp. 376 and 767 comparing the structures of chlorpheniramine with gabapentin. As any chemist would appreciate, the two structures are not equivalent. Further, chlorpheniramine is an antihistamine and gabapentin is an anticonvulsant.

Claims 1-2 and 5-6 are again rejected under 35 USC 103(a) as being unpatentable over *Bryans et al.* (U.S. 7,141,606) in view of *Berge et al.* (J. of Pharmaceutical Sciences, 66 no. 1, Jan. 1977, p. 1-19). Below are Applicants' arguments with regard to this rejection as submitted in Applicants' Response of July 23, 2007.

Bryans et al. disclose a method of treating insomnia by administering a therapeutically effective amount of (3S,4S)-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid or a pharmaceutically acceptable salt thereof. The compound recited above can be gabapentin. As the Examiner indicates, the present invention differs from Bryans et al. in that the formation of gabapentin tannate is not disclosed.

With regard to *Berge et al.*, Table I lists approximately 70 FDA-approved commercially marketed salts including tannate. It is interesting to note that of all the salts in use through 1974, tannate salts represented only 0.88% usage. The *Berge et al.* reference does not disclose gabapentin as a potential compound to be modified. (See Table III).

Specifically, regarding the rejection of claims 1-2 and 5-6 based on §103(a), the Examiner indicated that *Bryans et al.* expressly disclose that it seems reasonable to form the organic salt forms of gabapentin for sleep disorders based on col. 10, lines 33-37, which reads:

> Since amino acids are amphoteric, pharmacologically compatible salts when R is hydrogen can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, methanesulfonic acid, and ascorbic.

The Examiner then indicated that *Berge et al.* expressly describe various FDA-approved commercially marketed salts among which the tannate is displayed as one of the potential candidates for the pharmaceutical compounds. The Examiner then concludes that it would have been obvious to the skillful artisan in the art to be motivated to use the tannate for the salt of gabapentin for sleep disorders; this is because Berge et al. expressly teaches that one of the 70 FDA-approved commercially marketed salts can be the tannate.

Applicants respectfully traverse this rejection.

To establish a prima facie case of obviousness in light of the recent decision in *KSR International Co. v. Teleflex, Inc. and Technology Holding Co.*, No. 04-1350, 119 Fed. Appx. 282 (2007), in addition to the four criteria set forth in Graham v. John Deere Co., 383 U.S. 1148 USPQ 459 (1966), the Examiner must determine "whether there was an apparent reason to combine" the prior art references to derive the claimed invention. The reason to make the claimed combination must be found in the prior art, and not based on Applicants' disclosure. Failure to show any of the foregoing negates a prima facie showing of obviousness.

The invention as defined in claim 1 is gabapentin tannate. It is the Examiner's position that one skilled in the art would be able to just pick the tannate salt of the claimed invention from the laundry list provided in the *Berge et al.* reference. This is unlikely because even *Berge et al.* state that "choosing the appropriate salt ... can be a very difficult task, since each salt imparts

unique properties to the parent compound." (See page 1, col. 1, last sentence.) *Berge et al.* further state that "there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound." (See page 1, col. 2, lines 7-9.) Furthermore, the Examiner fails to appreciate that the most commonly used salt in *Berge et al.* is hydrochloride at 42.98% usage compared to tannate at 0.88% usage. Consequently, Applicants assert that the *Berge et al.* reference teaches away from combining gabapentin with tannic acid to produce gabapentin tannate.

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. Many inventions are combinations of old elements, and an Examiner may often find every element of a claimed invention in the prior art. If this finding were sufficient "to negate patentability, very few patents would ever issue." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Therefore, in order to establish a prima facie rejection for obviousness, an "examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed.Cir. 1998).

Taking into consideration the following:

1) *Bryans et al.* disclose gabapentin (not gabapentin tannate) for treating insomnia. There is no mention of a tannate salt of gabapentin in *Bryans et al.*

2) *Berge et al.* disclose a laundry list of FDA approved salts including tannate at a usage of 0.88% compared to a usage of 42.98% for hydrochloride salts with no mention of gabapentin; and

3) Applicants state in the present application that, while it is known that the formation of tannate salts with active pharmaceutical ingredients proceeds via a reaction of the

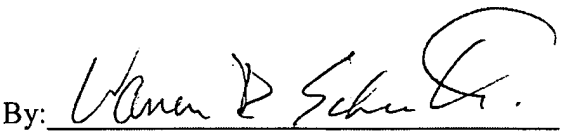
amine groups or other basic functional groups of the active ingredient with the carboxylic or hydroxyl group present in tannic acid. In the gabapentin compound, the close proximity of a carboxylic acid group to the positively charged amine functional group was expected to prevent the formation of the tannate salt. (See page 4, first full paragraph of the present specification.) Applicants submit that claims 1-2 and 5-6 are patentable over the cited references.

Applicants would like to bring to the attention of the Examiner that the prosecution history of the present application has been very inefficient with repeated disregard for several sections of the MPEP. For example, MPEP paragraphs 704.14(b) and 707.02 are particularly relevant. Applicants would also like to mention that the outstanding Office Action mailed September 24, 2007 is the seventh action in the prosecution of the present application.

Based on the arguments submitted above, the enclosed terminal disclaimer, and an apparent disregard of the MPEP throughout the prosecution history of the present application, Applicants request that claims 1, 2 and 5-21 be deemed allowable.

Respectfully submitted,

KING & SCHICKLI, PLLC

By: 

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APPENDIX I

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

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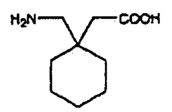
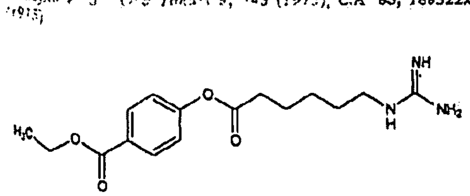
4342. Gabapentin. [60142-96-3] 1-(Aminomethyl)cyclohexaneacetic acid; CI-945; GO-3450; GOE-3450; Neurontin. $C_9H_{17}NO_2$; mol wt 171.24. C 63.13%, H 10.01%, N 8.18%, O 18.69%. Amino acid structurally related to γ-aminobutyric acid (GABA), q.v. designed to cross the blood brain barrier. Prepn: G. Satzinger et al., DE 2460891 (1976 to Gödecke); eidem, US 4024175 (1977 to Warner-Lambert). Pharmacokinetics and metabolism: K.-O. Vollmer et al., Arzneimittel-Forsch. 36, 830 (1986). Clinical pharmacology: B. Saletu et al., Int. J. Clin. Pharmacol. Ther. Toxicol. 24, 362 (1986). GC determn in biological fluids: W. D. Hooper et al., J. Chromatog. 529, 167 (1990). Review of pharmacology and clinical trials in epilepsy: B. Schmidt in Antiepileptic Drugs, R. H. Levy et al., Eds. (Raven Press, New York, 3rd ed., 1989) pp 925-935; K. L. Goa, E. M. Sorkin, Drugs 46, 409-427 (1993). Clinical trial for treatment of pain in diabetic neuropathy: M. Backonja et al., J. Am. Med. Assoc. 280, 1831 (1998). Clinical evaluation in social phobia: A. C. Pande et al., J. Clin. Psychopharmacol. 19, 341 (1999).



Crystals ... mp 162-166° (Satzinger); also reported as ... pKa₁ (25°) 3.68; pKa₂ 10.70. ... solubility in water at pH 7.4 exceeds ...%.

THERAP CAT: Anticonvulsant.

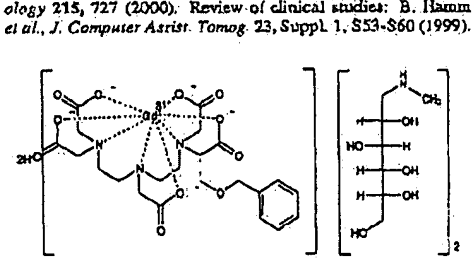
4343. Gabexate. [39492-01-8] 4-[[6-[(Aminoiminomethyl)amino]-1-oxohexyl]oxy]benzoic acid ethyl ester; p-hydroxybenzoic acid ethyl ester 6-guanidinohexanoate; p-carbethoxyphenyl ε-guanidinocaproate. $C_{16}H_{23}N_3O_4$; mol wt 321.37. C 59.80%, H 7.21%, N 13.08%, O 19.91%. Non-peptide proteolytic enzyme inhibitor which also inhibits the hydrolytic effects of thrombin, plasmin, and kallikrein, trypsin but not chymotrypsin; cf. aprotinin. Prepn as the p-toluenesulfonate salt: S. Fujii, T. Watanabe, DE 2050484; eidem, US 3751447 (1971, 1973 both to Ono). Enzyme inhibition: M. Muramatu, S. Fujii, Biochim. Biophys. Acta 268, 221 (1972); S. Tamura et al., ibid. 484, 417 (1977). Pharmacology: T. Okegawa et al., Nippon Yakurigaku Zasshi 71, 71 (1975), C.A. 84, 218m (1976). Metabolism: M. Sugiyama et al., Oyo Yakuri 9, 733 (1975), C.A. 83, 188145z (1975). Metabolism of inhibitory effect on platelet aggregation: G. Kosaki et al., Thromb. Res 20, 587 (1980). Beneficial action in traumatic shock: A. M. Lefer et al., IRCS Med. Sci. Libr. Compend. 8, 278 (1980); in exptl acute pancreatitis: ... Pancreas 2, 181 (1987). Comparative clinical study in acute pancreatitis: N. Tanaka et al., Adv. Exp. Med. Biol. 120, 567 (1979). Teratology and toxicity study: T. Fujita et al., Oyo Yakuri 9, 743 (1975), C.A. 83, 188322x (1975).



Methanesulfonate. [56974-61-9] Gabexate mesylate; FOY; Megacert. $C_{16}H_{23}N_3O_4.CH_3SO_3H$; mol wt 417.48. White crystals. Sol in water, ethanol, chloroform. Slightly sol in acetone. Practically insol in ether. pH of soln (1:100): 4.0-5.0. LD_{50} in mice (mg/kg): 8000 orally; 4700 s.c.; 25 i.v. (Fujita).

THERAP CAT: Enzyme inhibitor (proteinase).

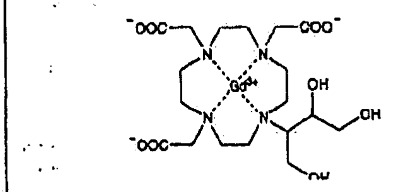
4344. Gadobenate Dimeglumine. [127000-20-8] 1-Deoxy-1-(methylamino)-D-glucitol [4-(carboxy-κO)-5,8,11-tris-[(carboxy-κO)methyl]-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5−)-κN^5,κN^8,κN^{11},κO^{13}]gadolinate(2−) (2:1); gadolinium benzyloxypropionictetraacetate dimeglumine; Gd-BOPTA/Dimeg; B-19036/7; MultiHance. $C_{36}H_{62}GdN_5O_{21}$; mol wt 1058.28. C 40.85%, H 5.92%, Gd 14.86%, N 6.62%, O 31.75%. $C_{22}H_{28}GdN_3O_{11}.2C_7H_{17}NO_5.2H$. Intravascular paramagnetic MRI contrast agent. Prepn: E. Felder et al., EP 230893; eidem, US 4916246 (1987, 1990 both to Bracco); F. Uggeri et al., Inorg. Chem. 34, 633 (1995). HPLC determn in biological samples: T. Arbughi et al., J. Chromatog. B 713, 415 (1998). Physicochemical properties: C. de Haën et al., J. Computer Assist. Tomog. 23, Suppl. 1, S161 (1999). Pharmacology: P. Tirone et al., ibid. S195. Pharmacokinetics: V. Lorusso et al., ibid. S181. Toxicology: A. Morisetti et al., ibid. S207. Clinical study in MRI of liver lesions: J. Petersein et al., Radiology 215, 727 (2000). Review of clinical studies: B. Hamm et al., J. Computer Assist. Tomog. 23, Suppl. 1, S53-S60 (1999).



Hygroscopic powder. mp 124°. Freely sol in water, sol in methanol. Practically insol in n-butanol, n-octanol, chloroform. Abs max 257.8 nm (ε 203). $[\alpha]^{20}_{546}$ −26.9° (c = 1.45 in water). Prepd as 0.5M soln, osmolality (37°) 1.97 mol/kg. d^{20} 1.22. Viscosity (mPa.s): 9.2 (20°), 5.3 (37°). LD_{50} i.v. in mice (mmol/kg): 5.7 (at 1 mL/min), 7.9 (at 0.2 mL/min); LD_{50} i.v. in rats (mmol/kg): 6.6 (at 6 mL/min), 9.2 (at 1 mL/min) (Morisetti).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4345. Gadobutrol. [138071-82-6] [10-[2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3−)-N^1,N^4,N^7,N^{10},O^1,O^4,O^7]gadolinium; Gd-DO3A-butrol; Gadovist. $C_{18}H_{31}GdN_4O_9$; mol wt 604.78. C 35.75%, H 5.18%, Gd 26.00%, N 9.27%, O 23.81%. Neutral macrocyclic gadolinium chelate. Prepn: J. Platzek et al., EP 448191 (1991 to Schering AG). Physicochemical properties and in vivo imaging studies: H. Vogler et al., Eur. J. Radiol. 21, 1 (1995). Clinical pharmacokinetics: T. Staks et al., Invest. Radiol. 29, 709 (1994). Clinical evaluation of diagnostic use for cerebral metastases: T. J. Vogl et al., Radiologe 35, 508 (1995); for glioblastomas: M. Hormann et al., Fortschr. Röntgenstr. 164, 119 (1996).



Hydrophilic. Osmolality (osmol/kg): 0.57 (0.5 mol/l); 1.39 (1 mol/l). Viscosity (cP): 1.43 (0.5 mol/l); 3.7 (1 mol/l). Partition coefficient (butanol/water): 0.006. LD_{50} i.v. in mice: 23 mmol/kg (Vogler).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4346. Gadodiamide. [131410-48-5] [5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-oato(3−)]gadolinium; gadolinium diethylene-